REMARKS

With the entry of the present amendment, claims 1-16 and 20-32 are in this application. Claim 16 has been amended to incorporate the limitations of claim 17, and claims 17-19 are canceled without prejudice. Support for additional amendments to claim 16 is found, for example, at Examples 1 and 2 of the as-filed application, which shows the steps for making the alphavirus replicon particle preparation. New claim 32 is supported by claim 13, for example. None of the amendments made herein constitutes the addition of new matter.

Telephone Interview Summary

In response to the Office Communication/Interview Summary mailed February 13, 2008, Applicants thank the Examiner for his willingness to discuss this application and for the insight he provided.

The undersigned urged that finality of the Office Action mailed October 4, 2007 was not appropriate in view of rejections made for the first time, which new rejections not being necessitated by any amendment made in the prior Amendment. The Examiner advised that Applicants should request withdrawal of finality. In addition, there was a discussion of "library", as noted in the Examiner's Summary. Finally, the undersigned discussed the advantages of the method by which the claimed libraries are made, in that libraries comprising rarely expressed sequences are enabled with the use of the salt wash method utilized in preparing the present claimed alphavirus replicon particle preparations.

Request for Withdrawal of Finality

Applicants respectfully request the withdrawal of finality of the present Office Action.

The present Office Action contains a new rejection under obviousness type double patenting, namely the rejection over US Patent 7,078,218, which issued in July 2006. The obviousness type double patent rejection also mentions Slovin et al. (1999) PNAS 96:5710-5715. This is a rejection which could have been made earlier, and Applicants respectfully maintain that it was not necessitated by any amendment provided in the response filed August 8, 2007.

Moreover, there were new Section 102 and Section 103 rejections over US Patent 7,078,218 made in the current office action as well, and this patent number was associated in the rejections with a name not in fact a part of the inventive entity of the patent. However, the '218 patent is not available as prior art; this patent has the same priority and filing dates as the instant application. Thus, not only were there new rejections made, but there is confusion resulting from the Examiner's association with "Johnston" with the cited patent number. If the number was not the piece of art intended to be cited, then the action taken and arguments made may have been different than those cited in the present Amendment. Applicants have proceeded with the understanding that the patent number was the intended citation and that "Johnston" was in error.

The Requirement for Restriction

The Patent Office has stated that the process claims of the same scope as allowable product claims may be rejoined but has said that rejoinder after final rejection is foreclosed.

Applicants respectfully point out that it is believed that finality of the current office action is not appropriate, as discussed above. Thus, no claims are cancelled at this time.

The Double Patenting Rejections

Claims 16-19 have been rejected on the ground of nonstatutory double patenting as allegedly unpatentable over claims 1-28 of US Patent 7,078,218. Applicants respectfully traverse this rejection.

While the claims of the cited patent provide for particularly efficient recovery of viral particles, the claims do not suggest the particular claimed products of the salt wash recovery method, which represent an expression library prepared from a tumor cell. However, in the interest of advancing prosecution and without acquiescing to this rejection, Applicants provide herewith a Terminal Disclaimer over the cited patent and payment of the necessary fee.

Claims 17 has been rejected on the ground of nonstatutory double patenting as allegedly unpatentable over claims 1-28 of US Patent 7,078,218 and also Slovin et al. (1999) Proc. Natl. Acad. Sci. USA96:5710-5715. Applicants respectfully traverse this rejection.

The Patent Office has stated that Slovin teaches that multiple carbohydrate antigens for a tumor may be used to develop multivalent vaccines and has concluded that it would have been obvious to modify the methods in developing a vaccine to prostate cancer.

Applicants respectfully submit that these statements of the Patent Office are formulated more like a Section 103 rejection than an obviousness-type double patenting rejection and that the cited patent is not prior art to the present application in view of the common filing and priority dates. However, as noted above, a Terminal Disclaimer over the cited patent is provided herewith.

Claims 16 and 18-19 remain rejected on the ground of nonstatutory double patenting as allegedly unpatentable over claim 6 of US Patent 7,090,852. Applicants respectfully traverse this rejection.

In the interest of advancing prosecution and without acquiescing to the rejection, Applicants have amended the claims to incorporate the limitations of claim 1 and to clarify that "the plurality of alphaviral replicon nucleic acids encode a plurality of antigens corresponding to a nucleic acid expression library synthesized from a tumor cell", with respect to the alphaviral replicon particle preparation.

Applicants respectfully submit that there is nothing in the claims of the cited patent which make obvious the presently claimed invention, which relies on a particular method to produce an alphavirus replicon particle preparation which encodes a plurality of antigens corresponding to an expression library from an antigen source of interest. In part, it is the salt wash step which allows the production of such an alphavirus replicon particle preparation which corresponds to an expression library. The salt wash step increases the number of particles from a single electroporation event by up to 2-3 orders of magnitude, thus allowing the recovery of alphavirus replicon particles encoding relatively rare expressed proteins from the antigen source of interest. This is not suggested by the claim of the cited patent. Thus, Applicants maintain that the present claimed particle preparations differ from those of the prior art in that the depth of the library which is possible using the salt wash method is greater than can be achieved using the prior art methods. A library of greater depth contains representatives of rarer members of the input population (for example, cDNAs prepared from the mRNA of a tumor cell). Furthermore, Hevey made a selection of replicon nucleic acids expressing specific antigens prior to producing the particles in the cited patent. Nothing in the '852 patent teaches or suggests a

preparation of particles made by employing a library of unselected, unidentified nucleic acid sequences.

In view of the foregoing and the amendments to the claims, the withdrawal of the rejection is respectfully requested.

Claims 16 and 18-19 have been rejected on the ground of nonstatutory double patenting as allegedly unpatentable over claims 2-3 and 8-9 of US Patent 6,783,939. Applicants respectfully traverse this rejection.

In the interest of advancing prosecution and without acquiescing to the rejection, Applicants have amended the claims to incorporate the limitations of claim 1 and to clarify that "the plurality of alphaviral replicon nucleic acids encode a plurality of antigens corresponding to a nucleic acid expression library synthesized from a tumor cell", with respect to the alphaviral replicon particle preparation.

Applicants respectfully submit that there is nothing in the claims of the cited patent which make obvious the presently claimed invention, which relies on a particular method to produce an alphavirus replicon particle preparation which encodes a plurality of antigens corresponding to an expression library from an antigen source of interest, i.e., a tumor cell. In part, it is the salt wash step which allows the production of such an alphavirus replicon particle preparation which corresponds to an expression library. The claims of the cited patent are strictly limited to three specific HIV antigens, and they would not make obvious the claimed preparation corresponding to an expression library from some other antigen source, such as a tumor cell.

In view of the foregoing, the withdrawal of the rejection is respectfully requested.

Claims 16 and 18-19 have been rejected on the ground of nonstatutory double patenting as allegedly unpatentable over claims 1, 3-8, 10-15, 33-40, 44-49 and 51-77 of US Patent 6,521,235. Applicants respectfully traverse this rejection.

In the interest of advancing prosecution and without acquiescing to the rejection, Applicants have amended the claims to incorporate the limitations of claim 1 and to clarify that "the plurality of alphaviral replicon nucleic acids encode a plurality of antigens corresponding to a nucleic acid expression library synthesized from a tumor cell", with respect to the alphaviral replicon particle preparation.

Applicants respectfully submit that there is nothing in the claims of the cited patent which make obvious the presently claimed invention, which relies on a particular method to produce an alphavirus replicon particle preparation which encodes a plurality of antigens corresponding to an expression library from an antigen source of interest. In part, it is the salt wash step which allows the production of such an alphavirus replicon particle preparation which corresponds to an expression library. The claims of the cited patent do not indicate that the population of particles corresponds to an expression library, such as that from a tumor cell, as set forth in the present application. Note the dependent claims that appear to indicate a single immunogen (or fragment).

In view of the foregoing, the withdrawal of the rejection is respectfully requested.

Claims 16 and 18-19 have been rejected on the ground of nonstatutory double patenting as allegedly unpatentable over claims 32, 34-35, 37, 40, 42, 44-45, 47, 50-52, 54-55, 57, 60, 62, 64-65, 67, 72, 74-75, 77, 80, 82 and 84-90 of US Patent 6,531,135. Applicants respectfully traverse this rejection.

In the interest of advancing prosecution and without acquiescing to the rejection, Applicants have amended the claims to incorporate the limitations of claim 1 and to clarify that "the plurality of alphaviral replicon nucleic acids encode a plurality of antigens corresponding to a nucleic acid expression library synthesized from a tumor cell", with respect to the alphaviral replicon particle preparation.

Applicants respectfully submit that there is nothing in the claims of the cited patent which make obvious the presently claimed invention, which relies on a particular method to produce an alphavirus replicon particle preparation which encodes a plurality of antigens corresponding to an expression library from an antigen source of interest. In part, it is the salt wash step which allows the production of such an alphavirus replicon particle preparation which corresponds to an expression library. The claims of the cited patent do not indicate that the population of particles corresponds to an expression library from an antigen source of interest, such as a tumor cell, as set forth in the present application and claims. Note that the claims of the cited patent appear to indicate that there can be more than one antigen expressed from a single alphavirus nucleic acid, but not that the population encodes antigens corresponding to an expression library from an antigen source of interest, as in the present application. In the present application, the population encompasses particles, which contain diverse replicon nucleic acids which represent the sequences expressed by the antigen source,

such as a tumor cell, while the cited patent contemplates a population of particles in which each particle contains the same replicon, whether it expresses one or multiple antigens.

In view of the foregoing, the withdrawal of the rejection is respectfully requested.

Claims 16 and 18-19 have been rejected on the ground of nonstatutory double patenting as allegedly unpatentable over claims 1-13, 16-17, 19, 23-35, 37-55, 57 and 61 of US Patent 6,156,558. Applicants respectfully traverse this rejection.

In the interest of advancing prosecution and without acquiescing to the rejection, Applicants have amended the claims to incorporate the limitations of claim 1 and to clarify that "the plurality of alphaviral replicon nucleic acids encode a plurality of antigens corresponding to a nucleic acid expression library synthesized from a tumor cell", with respect to the alphaviral replicon particle preparation.

Applicants respectfully submit that there is nothing in the claims of the cited patent which make obvious the presently claimed invention, which relies on a particular method to produce an alphavirus replicon particle preparation which encodes a plurality of antigens corresponding to an expression library from an antigen source of interest. In part, it is the salt wash step which allows the production of such an alphavirus replicon particle preparation which corresponds to an expression library. The claims of the cited patent do not indicate that the population of particles corresponds to an expression library from an antigen source of interest, as set forth in the present application and claims. Note that

the claims of the cited patent appear to indicate that there can be two antigens expressed from a single alphavirus nucleic acid, but not that the population encodes antigens corresponding to an expression library from an antigen source of interest, such as a tumor cell, as in the present application.

In view of the foregoing, the withdrawal of the rejection is respectfully requested.

Claims 16 and 18-19 have been rejected on the ground of nonstatutory double patenting as allegedly unpatentable over claims 22-26, 28-29, 31-34 and 36-37 of US Patent 6,541,010. Applicants respectfully traverse this rejection.

In the interest of advancing prosecution and without acquiescing to the rejection, Applicants have amended the claims to incorporate the limitations of claim 1 and to clarify that "the plurality of alphaviral replicon nucleic acids encode a plurality of antigens corresponding to a nucleic acid expression library synthesized from a tumor cell", with respect to the alphaviral replicon particle preparation.

Applicants respectfully submit that there is nothing in the claims of the cited patent which make obvious the presently claimed invention, which relies on a particular method to produce an alphavirus replicon particle preparation which encodes a plurality of antigens corresponding to an expression library from an antigen source of interest. In part, it is the salt wash step which allows the production of such an alphavirus replicon particle preparation which corresponds to an expression library. The claims of the cited patent do not indicate that the population of particles corresponds to an expression library from an antigen source of interest, as set forth in the present application and claims.

In view of the foregoing, the withdrawal of the rejection is respectfully requested.

Claims 16-19 have been provisionally rejected on the ground of nonstatutory obviousness-type double patenting as allegedly unpatentable over claims 1-21 of copending US Application 10/517,083. Applicants respectfully traverse this rejection.

As a first matter, Applicants respectfully submit that because the cited application is pending and has not been examined, the Patent Office should defer the rejection in the present application and should reinstitute the rejection if and when the cited application issues as a patent.

In the interest of advancing prosecution and without acquiescing to the rejection, Applicants have amended the claims to incorporate the limitations of claim 1 and to clarify that "the plurality of alphaviral replicon nucleic acids encode a plurality of antigens corresponding to an expression library for an antigen source", with respect to the alphaviral replicon particle preparation.

In any case, Applicants respectfully submit that there is nothing in the claims of the cited patent application which make obvious the presently claimed invention, which relies on a particular method to produce an alphavirus replicon particle preparation which encodes a plurality of antigens corresponding to an expression library from an antigen source of interest. In part, it is the salt wash step which allows the production of such an alphavirus replicon particle preparation which corresponds to an expression library. The claims of the cited patent application do not indicate that the population of particles corresponds to

an expression library from an antigen source of interest, such as that of a tumor cell as now claimed, and as set forth in the present application and claims. Note that the claims of the cited application appear to indicate that there can be more than one antigen expressed from a single alphavirus nucleic acid, but not that the population encodes antigens corresponding to an expression library from an antigen source of interest, as in the present application.

With respect to the statement that the instantly rejected claims are obvious over the claims and specification of the other application, Applicants respectfully note that the specification is not properly used in the formulation of a rejection for allegedly obviousness-type double patenting.

In view of the foregoing, the withdrawal of the rejection is respectfully requested.

Claims 16 and 18-19 have been provisionally rejected on the ground of nonstatutory double patenting as allegedly unpatentable over claims 2-9, 17-18, and 23-26 of US Application 10/929,234. The Examiner has deferred this rejection until either the present application or the cited application has been allowed.

In view of the foregoing, the withdrawal of the rejection is respectfully requested.

Claims 16-19 remain provisionally rejected on the ground of nonstatutory double patenting as allegedly unpatentable over claims 18, 24 and 25 of

copending US Application 11/132,711, and the Examiner has deferred this rejection until the present application or the cited application is allowed.

The Rejections under 35 U.S.C. 102

Claims 16 and 18-19 have been (newly) rejected under 35 U.S.C. 102(e) as allegedly anticipated by US Patent No. 7,078,218 to Johnston et al. Applicants respectfully traverse this rejection.

As a first matter, the cited patent is to Smith et al. The reference to Johnston et al. is not consistent with the patent number. Furthermore, the cited patent (cited by number) shares the same priority date (December 12, 2002) and the same filing date (December 12, 2003) as the present application. Thus, Applicants respectfully submit that this patent is not properly cited as prior art against the present application.

Even if the cited patent were prior art to the present application, it does not teach or disclose making an alphavirus replicon particle preparation using an expression library of nucleic acids to be incorporated into the viral replicon nucleic acids.

In view of the foregoing, Applicants respectfully maintain that the present invention as claimed is not anticipated by the cited reference, and thus, the rejection should be withdrawn.

Claims 16 and 18-19 have been rejected as allegedly anticipated by US Patent 6,521,235 (Johnston et al.). Applicants respectfully traverse this rejection.

In the interest of advancing prosecution and without acquiescing to the rejection, Applicants have amended the claims to incorporate the method steps from base claim 1 and to specify that the population of alphavirus replicon particles encodes antigens corresponding to an expression library from an antigen source of interest, from a tumor cell as now amended. An important aspect of the method used to produce the population of the present invention as claimed is the salt wash step, which allows one to obtain dramatically larger alphavirus replicon particle yields than was possible in prior art methods; this, at least in part, allows the production of a representative expression library, rather than one containing only the most abundantly expressed proteins from an antigen source of interest. Specifically, in the '235 patent, yields of ARPs in BHK cells were reported to range from 3×10^5 to 1×10^8 per ml (Column 15, line 43). Applicants found that yields from the methods taught in the '235 patent in Vero cells were the same or less than those obtained in BHK cells. In contrast, Applicants' method produced yields on the order of $10^{10} - 10^{11}$ (see Tables 1 and 2; paragraph [0056]), which are 2-3 orders of magnitude larger than the method practiced in the '235 patent. This is taught nowhere in the cited patent.

With respect to the allegation that the present inventors did not invent the claimed subject matter herein, it is stated on the record that they are the inventors for the presently claimed subject matter, as attested in the Inventors' Declaration accepted in this application.

In view of the foregoing, the instant claimed invention is not properly rejected under Section 102(e) or (f). Thus, Applicants respectfully request the withdrawal of this rejection.

Claims 16 and 18-19 have been rejected as allegedly anticipated by US Patent 7,090,852 (Hevey et al.). Applicants respectfully traverse this rejection.

In the interest of advancing prosecution and without acquiescing to the rejection, Applicants have amended the claims to incorporate the method steps from base claim 1 and to specify that the population of alphavirus replicon particles encodes antigens corresponding to an expression library from an antigen source of interest, i.e., a tumor cell. An important aspect of the method used to produce the population of the present invention as claimed is the salt wash step, which allows one to obtain dramatically larger alphavirus replicon particle yields than was possible in prior art methods; this, at least in part, allows the production of a representative expression library, rather than one containing only the most abundantly expressed proteins from an antigen source of interest. This is taught nowhere in the cited patent. Hevey et al. cited the 1997 publication of Pushko et al. for methods of packaging replicons into ARPs. This is the same method used by Johnston et al. ('235 patent discussed above) that resulted in yields that are orders of magnitudes lower than those claimed herein.

In addition, the cited patent appears to be limited to antigens related to Marburg virus, while the present application relates to a wide variety of antigen sources. The cited patent does not appear to teach or suggest a mixed population of alphavirus replicon particles, but rather single antigen-expressing populations or a population consisting of particles in which several antigens are expressed from a single nucleic acid. With respect to paragraph 5 in col. 7, it is not the same to say one or more particles derived from one or more replicon nucleic acids encoding one or more Marburg virion proteins. This is not what is claimed in the present invention, and nowhere does the cited patent appear to teach the creation of an expression library in alphavirus replicon particles using the methods incorporated into the claims.

In view of the foregoing, the instant claims as amended are not properly rejected under Section 102(e). Thus, Applicants respectfully request the withdrawal of this rejection.

Claims 16 and 18-19 have been rejected under 35 U.S.C. 102(e) as allegedly anticipated by US Patent 6,783,939 (Olmsted). Applicants respectfully traverse this rejection.

The Patent Office has referred to claims 2-3 and 8-9 of the cited patent as indicating that it teaches compositions of alphavirus replicon particles, comprising one or more encoded antigens from gag, pol and env.

In the interest of advancing prosecution and without acquiescing to the rejection, Applicants have amended the claims to incorporate the method steps from base claim 1 and to specify that the population of alphavirus replicon particles encodes antigens corresponding to an expression library from an antigen source of interest, namely a tumor cell. An important aspect of the method used to produce the population of the present invention as claimed is the salt wash step, which allows one to obtain dramatically larger alphavirus replicon particle yields than was possible in prior art methods; this, at least in part, allows the production of a representative expression library, rather than one containing only the most abundantly expressed proteins from an antigen source of interest. This is taught nowhere in the cited patent. Olmsted et al. teach a composition that comprises no more than three antigens, and these are specific clones that have been previously isolated and at least one of these antigens is modified in vitro from its native form, i.e. the form as it would appear in any expression library.

In view of the foregoing, Applicants respectfully maintain that the cited patent does not anticipate the instant invention as presently claimed, and the rejection must be withdrawn.

Claims 16 and 18-19 have been rejected under 35 U.S.C. 102(e) as allegedly anticipated by US Patent 6,521,235 (Johnston et al.). Applicants respectfully traverse this rejection.

The Patent Office has stated that claims 3-4 of the cited patent relate to alphavirus replicon vectors that encode one or more antigens and may be of viral, protozoan or bacterial origin.

In the interest of advancing prosecution and without acquiescing to the rejection, Applicants have amended the claims to incorporate the method steps from base claim 1 and to specify that the population of alphavirus replicon particles encodes antigens corresponding to an expression library from an antigen source of interest, namely that of a tumor cell. An important aspect of the method used to produce the population of the present invention as claimed is the salt wash step, which allows one to obtain dramatically larger alphavirus replicon particle yields than was possible in prior art methods; this, at least in part, allows the production of a representative expression library, rather than one containing only the most abundantly expressed proteins from an antigen source of interest. This is taught nowhere in the cited patent, and the methods taught by Johnston et al. (as discussed hereinabove) do not provide sufficient yield to enable, let alone anticipate the present invention as claimed. At Column 8, line 61 through Column 9, line 8, Johnston et al. describe how they would accomplish vaccination with “two immunogens”, which consists of two immunogens operably

linked to separate control elements (i.e. a promoter or an IRES) included in a single replicon. This is not a strategy that would be feasible for expressing a library of nucleic acids.

In view of the foregoing, Applicants respectfully maintain that the cited patent does not anticipate the instant invention as presently claimed, and the rejection must be withdrawn.

Claims 16 and 18-19 have been rejected under 35 U.S.C. 102(e) as allegedly anticipated by US Patent 6,531,135 (Johnston et al.). Applicants respectfully traverse this rejection.

The Patent Office has stated that the cited patent teaches alphaviral replicon particles encoding more than one antigen (claims 34-35) which may be from several viral sources (e.g, col. 5). Applicants note that the '135 patent is a continuation of the issued '235 patent discussed hereinabove, and claims 34-35 of the '135 patent are analogous to claims 3-4 of the '235 patent, and the specifications are identical. Thus, the arguments made above with respect to the '235 patent apply directly to this rejection.

In the interest of advancing prosecution and without acquiescing to the rejection, Applicants have amended the claims to incorporate the method steps from base claim 1 and to specify that the population of alphavirus replicon particles encodes antigens corresponding to an expression library from a tumor cell. An important aspect of the method used to produce the population of the present invention as claimed is the salt wash step, which allows one to obtain dramatically larger alphavirus replicon particle yields than was possible in prior art methods; this, at least in part, allows the production of a representative

expression library, rather than one containing only the most abundantly expressed proteins from an antigen source of interest. This is taught nowhere in the cited patent. The cited portion of the Johnston et al. patent teaches nothing about an expression library or the recited method of making such a population of alphavirus replicon particles.

In view of the foregoing, Applicants respectfully maintain that the cited patent does not anticipate the instant invention as presently claimed, and the rejection must be withdrawn.

Claims 16 and 18-19 have been rejected under 35 U.S.C. 102(a) as allegedly anticipated by US Patent 6,495,143 and US 2002/0034521 (Lee et al.). Applicants respectfully traverse this rejection.

The Patent Office has stated that the cited patent teaches alphaviral replicon particles encoding a plurality of botulinum bacteria antigens (e.g, claim 28).

In the interest of advancing prosecution and without acquiescing to the rejection, Applicants have amended the claims to incorporate the method steps from base claim 1 and to specify that the population of alphavirus replicon particles encodes antigens corresponding to an expression library from a tumor cell. An important aspect of the method used to produce the population of the present invention as claimed is the salt wash step, which allows one to obtain dramatically larger alphavirus replicon particle yields than was possible in prior art methods; this, at least in part, allows the production of a representative expression library, rather than one containing only the most abundantly expressed proteins from an antigen source of interest. This is taught nowhere in

the cited patent. Applicants note that the cited claim includes a maximum of 6 encoded antigens, which is nowhere near a representative library of an antigen source such as *Clostridium botulinum*, a tumor or a pathogenic microorganism.

In view of the foregoing, Applicants respectfully maintain that the cited patent does not anticipate the instant invention as presently claimed, and the rejection must be withdrawn.

Claims 16 and 18-19 have been rejected under 35 U.S.C. 102(e) as allegedly anticipated by US Patent 6,632,640 (Lee et al.). Applicants respectfully traverse this rejection.

The Patent Office has stated that the cited patent teaches alphaviral replicon particles encoding two distinct antigens of *Staphylococcus aureus* exotoxins [sic] (e.g, col. 3, paragraphs 2-3).

In the interest of advancing prosecution and without acquiescing to the rejection, Applicants have amended the claims to incorporate the method steps from base claim 1 and to specify that the population of alphavirus replicon particles encodes antigens corresponding to an expression library from a tumor cell. An important aspect of the method used to produce the population of the present invention as claimed is the salt wash step, which allows one to obtain dramatically larger alphavirus replicon particle yields than was possible in prior art methods; this, at least in part, allows the production of a representative expression library, rather than one containing only the most abundantly expressed proteins from an antigen source of interest. This is taught nowhere in the cited patent. Applicants note that the cited passage appears to relate to two

encoded antigens, which is nowhere near a representative library of an antigen source such as a tumor cell.

In view of the foregoing, Applicants respectfully maintain that the cited patent does not anticipate the instant invention as presently claimed, and the rejection must be withdrawn.

Claims 16 and 18-19 have been rejected under 35 U.S.C. 102(e) as allegedly anticipated by US Patent 6,770,479 (Lee et al.). Applicants respectfully traverse this rejection.

The Patent Office has stated that the cited patent teaches a composition of VEE replicons encoding more than one antigen of anthrax (e.g, claim 15).

In the interest of advancing prosecution and without acquiescing to the rejection, Applicants have amended the claims to incorporate the method steps from base claim 1 and to specify that the population of alphavirus replicon particles encodes antigens corresponding to an expression library from a tumor cell. An important aspect of the method used to produce the population of the present invention as claimed is the salt wash step, which allows one to obtain dramatically larger alphavirus replicon particle yields than was possible in prior art methods; this, at least in part, allows the production of a representative expression library, rather than one containing only the most abundantly expressed proteins from the antigen source of interest (tumor cell). This is taught nowhere in the cited patent. Applicants note that the cited claim appears to relate to four encoded antigens, which is nowhere near a representative library of an antigen source such as a tumor cell.

In view of the foregoing, Applicants respectfully maintain that the cited patent does not anticipate the instant invention as presently claimed, and the rejection must be withdrawn.

Claims 16 and 18-19 have been rejected under 35 U.S.C. 102(a) as allegedly anticipated by US Publication 2002/0164582 (Hart et al.). Applicants respectfully traverse this rejection.

The Patent Office has stated that the cited patent teaches a composition of VEE replicons encoding antigens of Ebola virus (e.g, claim 59 and paragraph 0025).

In the interest of advancing prosecution and without acquiescing to the rejection, Applicants have amended the claims to incorporate the method steps from base claim 1 and to specify that the population of alphavirus replicon particles encodes antigens corresponding to an expression library from a tumor cell. An important aspect of the method used to produce the population of the present invention as claimed is the salt wash step, which allows one to obtain dramatically larger alphavirus replicon particle yields than was possible in prior art methods; this, at least in part, allows the production of a representative expression library, rather than one containing only the most abundantly expressed proteins from an antigen source of interest. This is taught nowhere in the cited patent. Applicants note that the cited paragraph 25 refers to a limited number of encoded antigens (paragraph 0013 appears to refer to 6), which is not believed to be a representative library of an antigen source such as a tumor cell.

In view of the foregoing, Applicants respectfully maintain that the cited patent does not anticipate the instant invention as presently claimed, and the rejection must be withdrawn.

Claims 16 and 18-19 have been rejected under 35 U.S.C. 102(e) as allegedly anticipated by US Patent 6,517,842 (Hevey et al.). Applicants respectfully traverse this rejection.

The Patent Office has stated that the cited patent teaches a composition of VEE replicons encoding more than one antigen of Marburg virus (e.g., col. 3, paragraph 4).

In the interest of advancing prosecution and without acquiescing to the rejection, Applicants have amended the claims to incorporate the method steps from base claim 1 and to specify that the population of alphavirus replicon particles encodes antigens corresponding to an expression library from a tumor cell. An important aspect of the method used to produce the population of the present invention as claimed is the salt wash step, which allows one to obtain dramatically larger alphavirus replicon particle yields than was possible in prior art methods; this, at least in part, allows the production of a representative expression library, rather than one containing only the most abundantly expressed proteins from an antigen source of interest. This is taught nowhere in the cited patent. Applicants note that the cited claim appears to relate to seven encoded proteins, which is not believed to be a representative library of an antigen source such as a tumor cell.

In view of the foregoing, Applicants respectfully maintain that the cited patent does not anticipate the instant invention as presently claimed, and the rejection must be withdrawn.

Claims 16 and 18-19 have been rejected under 35 U.S.C. 102(e) as allegedly anticipated by US Patent 6,156,558 (Johnston et al.). Applicants respectfully traverse this rejection.

The Patent Office has stated that the cited patent teaches a plurality of alphavirus particles encoding a plurality of antigens (e.g, col. 5).

In the interest of advancing prosecution and without acquiescing to the rejection, Applicants have amended the claims to incorporate the method steps from base claim 1 and to specify that the population of alphavirus replicon particles encodes antigens corresponding to an expression library from a tumor cell. An important aspect of the method used to produce the population of the present invention as claimed is the salt wash step, which allows one to obtain dramatically larger alphavirus replicon particle yields than was possible in prior art methods; this, at least in part, allows the production of a representative expression library, rather than one containing only the most abundantly expressed proteins from the antigen source of interest. This is taught nowhere in the cited patent. Applicants note that the cited passage appears to relate to certain viruses, but it does not appear to teach or suggest that encoded antigens corresponding to a representative library of a tumor cell is incorporated into a population of alphavirus replicon particles using the methodology recited in the instant claims.

In view of the foregoing, Applicants respectfully maintain that the cited patent does not anticipate the instant invention as presently claimed, and the rejection must be withdrawn.

Claims 16 and 18-19 have been rejected under 35 U.S.C. 102(e) as allegedly anticipated by US Patent 6,451,592 (Dubensky et al.). Applicants respectfully traverse this rejection.

The Patent Office has stated that the cited patent teaches a composition of alphavirus replicons comprising multiple heterologous sequences (e.g., col. 3, paragraph 4; cols. 33-34, bridging paragraph).

In the interest of advancing prosecution and without acquiescing to the rejection, Applicants have amended the claims to incorporate the method steps from base claim 1 and to specify that the population of alphavirus replicon particles encodes antigens corresponding to an expression library from a tumor cell. An important aspect of the method used to produce the population of the present invention as claimed is the salt wash step, which allows one to obtain dramatically larger alphavirus replicon particle yields than was possible in prior art methods; this, at least in part, allows the production of a representative expression library, rather than one containing only the most abundantly expressed proteins from the antigen source of interest. This is taught nowhere in the cited patent. It appears to Applicants that the cited paragraph relates to a single alphaviral nucleic acid molecule engineered to express more than one antigen or nucleic acid. The context does not teach or suggest a population corresponding to an expression library. The second cited paragraph similarly appears to lack such a teaching.

In view of the foregoing, Applicants respectfully maintain that the cited patent does not anticipate the instant invention as presently claimed, and the rejection must be withdrawn.

Claims 16 and 18-19 have been rejected under 35 U.S.C. 102(e) as allegedly anticipated by US Patent 5,792,462 (Johnston et al.). Applicants respectfully traverse this rejection.

The Patent Office has stated that the cited patent teaches a composition of VEE replicons encoding more than one Lassa fever virus protein (Example 4).

In the interest of advancing prosecution and without acquiescing to the rejection, Applicants have amended the claims to incorporate the method steps from base claim 1 and to specify that the population of alphavirus replicon particles encodes antigens corresponding to an expression library from a tumor cell. An important aspect of the method used to produce the population of the present invention as claimed is the salt wash step, which allows one to obtain dramatically larger alphavirus replicon particle yields than was possible in prior art methods; this, at least in part, allows the production of a representative expression library, rather than one containing only the most abundantly expressed proteins from the antigen source of interest. This is taught nowhere in the cited patent. It appears to Applicants that the cited Example (4) relates to coding sequences separately cloned into a VEE replicon nucleic acid, and the introduction of an alphaviral nucleic acid molecule encoding a single Lassa fever antigen (with two helper nucleic acids) into BHK cells. The Lassa fever antigen-encoding preparation then was administered to mice, where an immune response was triggered. The context does not teach or suggest a population corresponding to an expression library.

In view of the foregoing, Applicants respectfully maintain that the cited patent does not anticipate the instant invention as presently claimed, and the rejection must be withdrawn.

The Rejections under 35 U.S.C. 103

Claims 16-17 have been rejected under 35 U.S.C. 103(a) as allegedly unpatentable over 7,078,218 to Johnston et al. and Slovin et al. (1999) PNAS 96:5710-5715. Applicants respectfully traverse this rejection.

The Patent Office has noted an inventor in common between the cited patent and the present application and refers to an earlier filing date of the patent.

Applicants respectfully note that the patent number cited in the rejection is not to Johnston et al., but rather to Smith et al. The cited '218 patent is assigned to the same assignee as in the present application, and it claims benefit to the same priority/provisional filing date (December 12, 2002) and it has the same filing date as the present application (December 12, 2003). Thus, the '218 patent is not prior art to the present application, and the application is not proper and must be withdrawn. In addition, the Slovin reference relates to chemically synthesized carbohydrate antigens associated with cancer. Applicants do not see the relevance in that it does not relate either to polypeptide antigens, which can be expressed from a nucleic acid encoded by an alphavirus replicon nucleic acid, or to alphavirus replicon particles in the context of the present claims. Thus, Applicants respectfully submit that there has been no prima facie case for obviousness made and the rejection should be withdrawn.

Claims 16-17 have been rejected under 35 U.S.C. 103 as allegedly unpatentable over US Patent 6,156,558 (Johnston), Nestle et al. (1998) and Smooker (2000). Applicants respectfully traverse this rejection.

The cited Johnston reference is said to teach the use of similar alphavirus particles in vaccines and to demonstrate that particles are sufficient to produce immune responses against foreign gene encoded proteins, but Johnston is acknowledged to lack the teaching of a plurality of antigens or the use of cancer antigens.

Nestle is said to teach a cocktail of peptides used to produce cancer immunity and Smooker is said to demonstrate that a library of epitopes may be administered to develop an immune response. The Patent Office has concluded that it would have been obvious to make a plurality of alphaviral replicons encoding the different peptides of Nestle and that the artisan would have been motivated to do so to produce an immune response to cancer, using the method of Smooker instead of actual delivery of the polypeptides. It is also alleged that there would have been a reasonable expectation of success as Smooker had demonstrated that a plurality of antigens could have been delivered and Nestle taught that the plurality of peptides produced immune response to cancer.

In the interest of advancing prosecution and without acquiescing to the rejection, Applicants have amended the claims to incorporate the method steps from base claim 1 and to specify that the population of alphavirus replicon particles encodes antigens corresponding to an expression library from a tumor cell. An important aspect of the method used to produce the population of the present invention as claimed is the salt wash step, which allows one to obtain dramatically larger alphavirus replicon particle yields (up to two to three orders of

magnitude) than was possible in prior art methods; this, at least in part, allows the production of a representative expression library, rather than one containing only the most abundantly expressed proteins from an antigen source of interest. This leads to the production of a preparation of alphavirus replicon particles which is surprisingly improved over the prior art.

The Smooker reference teaches the creation of a secreted peptide expression library to be administered as a DNA preparation; at page 2535 it is stated that the majority of in-frame peptides were less than 20 amino acids and 13% were greater than 50 amino acids, with a range from 1-115. Thus, the library is one of partial proteins, and by virtue of the necessity for in frame fusions, only 1 in 6 clones represents a portion of a protein expressed in the antigen source (i.e. Plasmodium). This is a very different approach than is taken in the present Specification or is claimed in this application.

The cited Nestle reference relates to vaccination of melanoma patients with peptide or tumor lysate pulsed dendritic cells. This reference does not teach or suggest the use of any sort of **tumor cell expression library** for immunizing a patient.

Combining the cited references, in the absence of hindsight could give a DNA vector for expressing melanoma antigens, an alphavirus system for expressing a plasmodium peptide library, a lysate of plasmodium or single preparations for expressing hemagglutinin, green fluorescent protein, or Lassa fever N antigen or the proteins themselves. There is nothing that would point the way to the present claimed invention, especially in view of the relatively low recovery of the alphavirus replicon particles prior to present Applicants' discovery of the dramatic increase in yield with the use of a salt wash for alphavirus particles which are characterized by heparin binding.

In view of the foregoing, Applicants respectfully submit that the invention as claimed is not prima facie obvious over the cited art, and the withdrawal of the rejection is requested.

Claims 16 and 18-19 have been rejected under 35 U.S.C. 103 as allegedly unpatentable over US Patent 6,156,558 (Johnston) and Smooker (2000). Applicants respectfully traverse this rejection.

Johnston is said to have taught the use of similar alphaviral particles in vaccines and that the particles are sufficient to produce immune responses against foreign gene encoded proteins, but Johnston is acknowledged not to teach the use of a plurality of antigens or the use of antigens to protozoans. Smooker is said to teach a library of epitopes expressed on separate plasmids (a library) for immunizing mice against Plasmodium, a protozoan. The Patent Office has concluded that it would have been obvious to make a library of alphavirus replicon particles encoding different foreign antigens of the protozoan, that the artisan would have been motivated to do so to immunize mice and that there would have been a reasonable expectation of success.

In the interest of advancing prosecution and without acquiescing to the rejection, Applicants have amended the claims to incorporate the method steps from base claim 1 and to specify that the population of alphavirus replicon particles encodes antigens corresponding to an expression library from a tumor cell. An important aspect of the method used to produce the population of the present invention as claimed is the salt wash step, which allows one to obtain dramatically larger alphavirus replicon particle yields than was possible in prior art methods; this, at least in part, allows the production of a representative

expression library, rather than one containing only the most abundantly expressed proteins from an antigen source of interest.

In view of the foregoing, Applicants submit that the presently claimed invention is not *prima facie* obvious over the cited references, and the withdrawal is respectfully requested.

Claims 16 and 18-19 have been rejected under 35 U.S.C. 103 as allegedly unpatentable over US Patent 6,235,290 (Brunham), US Patent 6,156,558 (Johnston) and Smooker (2000). Applicants respectfully traverse this rejection.

Brunham is said to teach a DNA vaccine against Chlamydia and the design of a multivalent vaccine using various forms of the MOMP gene to provide increased immunity of more strains of Chlamydia. Johnston is said to teach the use of similar alphavirus replicon particles in vaccines and that the particles are sufficient to produce an immune response against foreign gene encoded proteins. Smooker is said to teach a library of Plasmodium epitopes expressed via a plasmid library. The Patent Office has concluded that it would have been obvious to modify the Brunham composition to contain MOMP antigens in the Johnston vectors, that there was motivation to increase the number of Chlamydia strains to which an immune response is elicited and that the artisan would have had reasonable expectation of success as Smooker had taught that large libraries of peptides elicited immunity when administered as a DNA vaccine.

The cited Johnston and Smooker references have been discussed above. The Brunham reference does not teach the need for immunizing with more than one protein from the antigen source, i.e., a major outer membrane protein from Chlamydia. Based on the teachings of the three cited references, it would be

more likely that one of ordinary skill in the art would have been motivated to express the MOMP in an alphavirus or to make an epitope library using the MOMP coding sequence(s) as starting materials. Brunham teaches that a "possibly more feasible way is to design a multivalent vaccine based on multiple MOMP genes". Since Brunham only teaches a single MOMP gene on each DNA molecule, the only permissible inference of the suggestion of Brunham is to construct several different DNA vectors, each capable of expressing a different MOMP gene and then make a cocktail of these individually selected and synthesized DNA vectors. This approach was acknowledged by Applicants in the instant application as encompassed in the existing art and is quite distinct from the invention as currently claimed. Applicants do not see that it would have been obvious to make a representative expression library of a tumor cell using alphavirus replicon particles based on these references. In addition, as noted above, prior art methods for collecting alphavirus particles did not allow for the improved yields only enabled in the present disclosure (and in US Patent 7,078,218, filed on even date herewith and commonly assigned). A critical step is the salt wash for collecting the alphaviral particles which are characterized by the ability to bind heparin.

In the interest of advancing prosecution and without acquiescing to the rejection, Applicants have amended the claims to incorporate the method steps from base claim 1 and to specify that the population of alphavirus replicon particles encodes antigens corresponding to an expression library from a tumor cell. An important aspect of the method used to produce the population of the present invention as claimed is the salt wash step, which allows one to obtain dramatically larger alphavirus replicon particle yields than was possible in prior art methods; this, at least in part, allows the production of a representative expression library, rather than one containing only the most abundantly expressed proteins from an antigen source of interest.

The cited Brunham patent teaches DNA immunization as a means to elicit an immune response, in particular to a major outer membrane protein of Chlamydia. There is no teaching of a variety of antigens (only fragments or variations of the particular chlamydial MOMP). In that Brunham teaches a distinct approach (DNA immunization, single target antigen) from that of the present claimed invention (alphavirus replicon particle, representative expression library, preparation made in a particular high efficiency way, i.e., with salt wash to significantly increase particle yield), the cited Brunham reference should be viewed as teaching away from the present claimed invention. Similarly, Smooker teaches away from the present claimed invention in that there is a peptide epitope plasmid library. Johnston, with its teaching of a limited teaching of alphavirus replicon particles and immune responses, would not appear to trump the alternate approaches of Brunham and Smooker in the absence of the impermissible use of hindsight.

In view of the foregoing, Applicants respectfully maintain that the present invention as claimed is not prima facie obvious over the cited references and request that the rejection should be withdrawn.

Claims 16-19 have been rejected under 35 U.S.C. 103 as allegedly unpatentable over US Patent 5,866,553 (Donnelly), US Patent 6,156,558 (Johnston) and Smooker (2000). Applicants respectfully traverse this rejection.

Donnelly is said to have taught immune responses to papilloma virus via DNA constructs encoding papilloma gene products. The patent office has concluded that because several antigens are taught which may be used in combination immunization was against cancer. Johnston is said to teach the use

of similar alphavirus replicon particles in vaccines and that the particles are sufficient to produce an immune response against foreign gene encoded proteins. Smooker is said to teach a library of Plasmodium epitopes expressed via a plasmid library. The Patent Office has concluded that it would have been obvious to modify the composition of Donnelly to contain different antigens of HPV in the alphaviruses of Johnston, that there was motivation to provide immunity to HPV and cancer and that the artisan would have had a reasonable expectation of success as Smooker had taught libraries of particles could elicit immunity.

In the interest of advancing prosecution and without acquiescing to the rejection, Applicants have amended the claims to incorporate the method steps from base claim 1 and to specify that the population of alphavirus replicon particles encodes antigens corresponding to an expression library from a tumor cell. An important aspect of the method used to produce the population of the present invention as claimed is the salt wash step, which allows one to obtain dramatically larger alphavirus replicon particle yields than was possible in prior art methods; this, at least in part, allows the production of a representative expression library, rather than one containing only the most abundantly expressed proteins from an antigen source of interest.

Donnelly appears to teach monovalent and multivalent vaccines for preventing PV infection. The monovalent vaccine may be made by formulating DNA encoding HPV16 L1 protein or L2 protein, or L1 + L2 proteins. Alternatively, a multivalent HPV vaccine may be formulated by mixing DNA encoding L1 or L2 or L1+L2 proteins from different HPV types". Thus, Donnelly at most teaches 2 selected antigens in a given construct and teaches making cocktails of different constructs to achieve "multivalent' vaccines. Smooker teaches the expression of peptide epitopes via a plasmid library. Both of these approaches are different

from that of present Applicants, and thus can be considered to teach away from the alphavirus replicon particle expression library approach. Johnston teaches the alphavirus replicon particle approach, but does not teach the use of the method steps recited in the claims as amended to prepare a particle preparation. These steps (notably the salt wash step) allow the production of a significantly larger number of particles from a comparable attempt and thus, the production of a representative expression library where the possible members are numerous. It is only by hindsight reconstruction that the Examiner could have selected various aspects from the cited references to arrive at the obviousness rejection. In addition, the particles of Smooker were biolistic particles with a DNA vector, not the alphavirus particles of the present invention, which actually are believed to allow for more efficient expression due to the ability of the virus envelope proteins to facilitate entry into cells. In addition, the viral proteins are thought to target the replicon nucleic acid to dendritic cells, thus further facilitating the development of an immune response.

Claims 16 and 18-19 have been rejected under 35 U.S.C. 103 as allegedly unpatentable over US Patent 6,309,642 (Cutler), US Patent 6,156,558 (Johnston) and Smooker (2000). Applicants respectfully traverse this rejection.

Cutler is said to teach several antigens designed to elicit immunity to Candida delivered by polynucleotides encoding the antigens. Johnston is said to teach the use of similar alphavirus replicon particles in vaccines and that the particles are sufficient to produce an immune response against foreign gene encoded proteins. Smooker is said to teach a library of Plasmodium epitopes expressed via a plasmid library. The Patent Office has concluded that it would have been obvious to modify the methods of Cutler by making several alphaviral replicon particles of Johnston to encode different antigens taught by Cutler, that there was motivation to provide immunity to Candida as Johnston taught such

DNA immunization would provide similar immunity and that the artisan would have had a reasonable expectation of success as Smooker had taught libraries of particles could elicit immunity.

In the interest of advancing prosecution and without acquiescing to the rejection, Applicants have amended the claims to incorporate the method steps from base claim 1 and to specify that the population of alphavirus replicon particles encodes antigens corresponding to an expression library from a tumor cell. An important aspect of the method used to produce the population of the present invention as claimed is the salt wash step, which allows one to obtain dramatically larger alphavirus replicon particle yields than was possible in prior art methods; this, at least in part, allows the production of a representative expression library, rather than one containing only the most abundantly expressed proteins from an antigen source of interest.

Applicants note that the Cutler patent teaches the use of **peptides** which mimic carbohydrate (mannan) epitopes from **Candida** as immunogens; see col. 4, lines 12-19. There is extensive disclosure related to the limited scope of this actual antigenic target in this patent. This appears to be a very specific subset of epitopes associated with Candida and not relevant to the invention as claimed in the present application. In Cutler, the peptides are mimics of carbohydrate antigens – they do not correspond in structure to a naturally occurring polypeptide antigen, which is the object of the alphavirus replicon particle expression of the instant claimed invention.

It is not believed that the teaching of Cutler combined with those of the other two references would lead one to the present claimed invention in the absence of the use of hindsight. Rather it might be likely that the encoded peptides might be presented as a DNA vaccine or a particular mimotope might

be expressed by an alphavirus vector. In any case, there was no enabling disclosure as to the particular method used to produce the alphaviral replicon particle preparation of the instant claimed invention with its salt wash step.

In view of the foregoing, Applicants respectfully maintain that claimed invention (as amended) is not prima facie obvious over the cited references, and the withdrawal of the rejection is requested.

Conclusion

In view of the foregoing, it is submitted that this case is in condition for allowance, and passage to issuance is respectfully requested.

If there are any outstanding issues related to patentability, the courtesy of a telephone interview is requested, and the Examiner is invited to call to arrange a mutually convenient time.

This amendment is accompanied by a Terminal Disclaimer and a Petition for Extension of Time (three months) with authorization to charge the amount of $1180.00, as required under 37 C.F.R. 1.17(a) ($1050.00 for extension of time) and under 37 C.F.R. 1.20(d) ($130.00 for Disclaimer fee). It is believed that this response does not necessitate the payment of any additional fees under 37 C.F.R. 1.16-1.17 or any additional extension of time. If the amount submitted is incorrect, however, please charge the necessary amount due under the foregoing Rules to Deposit Account No. 07-1969.

Respectfully submitted,

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